PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
60161/SGW/AW		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/DK 99/ 00522	04/10/1999	
Applicant		
DAMGAARD, Lars, Riis et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

   [X] as suggested by the applicant.

   [ ] None of the figures.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00522

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PC[redacted]K 99/00522

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B5/0275 G01F1/704

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61B G01N G01F G01P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 46853 A (UNISENSE) 11 December 1997 (1997-12-11) abstract; figures 1,2 page 4, line 2-14 page 7, line 20-30 page 8, line 35 -page 9, line 34	7,8
A	WO 97 19345 A (DAMGAARD LARS RIIS ;REVSBECH NIELS PETER) 29 May 1997 (1997-05-29) abstract; figure 1 page 4, line 15-19 page 6, line 17-27 page 7, line 24-31	7
A	WO 95 16392 A (MODERN TECHNOLOGIES CORP) 22 June 1995 (1995-06-22) abstract	7

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 May 2000	06/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Jonsson, P.O.

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PC[redacted]K 99/00522

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 549 394 A (HEMODIA SOCIETE ANONYME) 30 June 1993 (1993-06-30) abstract; figure 1 column 3, line 23-35	7,8
A	US 5 594 179 A (MARSH LAWRENCE B) 14 January 1997 (1997-01-14) abstract; figure 1	7
A	EP 0 747 675 A (AIR LIQUIDE) 11 December 1996 (1996-12-11) abstract	7
A	WO 98 59240 A (AROMASCAN PLC) 30 December 1998 (1998-12-30) abstract; figure 2	14

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PC[redacted]X 99/00522

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9746853 A	11-12-1997	DK 63396 A	07-12-1997
		AU 3090597 A	05-01-1998
		EP 0902881 A	24-03-1999
WO 9719345 A	29-05-1997	AU 7621496 A	11-06-1997
		EP 0882225 A	09-12-1998
		JP 2000500580 T	18-01-2000
		US 6030828 A	29-02-2000
WO 9516392 A	22-06-1995	US 5439003 A	08-08-1995
		AU 690602 B	30-04-1998
		AU 1099195 A	03-07-1995
		BR 9408349 A	26-08-1997
		EP 0734225 A	02-10-1996
		US 5724982 A	10-03-1998
EP 0549394 A	30-06-1993	FR 2684864 A	18-06-1993
US 5594179 A	14-01-1997	NONE	
EP 0747675 A	11-12-1996	US 5672827 A	30-09-1997
		BR 9602672 A	06-10-1998
		CA 2178533 A	08-12-1996
		JP 9105656 A	22-04-1997
WO 9859240 A	30-12-1998	NONE	

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70) 12

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
72790/UvF/Sp		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK99/00522	04/10/1999	04/10/1999
International Patent Classification (IPC) or national classification and IPC A61B5/0275		
Applicant DAMGAARD, Lars, Riis et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12/04/2001	11.01.2002
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Abraham, V Telephone No. +49 89 2399 7463

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK99/00522

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

5-10	as originally filed	
1-4	with telefax of	01/10/2001

Claims, No.:

1-10	with telefax of	01/10/2001

Drawings, sheets:

1/6-6/6	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-10
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations
   see separate sheet

Reference is made to the following document:
D1: WO 97 46853 A (UNISENSE) 11 December 1997

V

1. Document D1 which is considered to represent the most relevant prior art discloses the following features of claim 1:

   Sensor for the measurement of tissue perfusion (Fig. 2) comprising a reservoir (2) for containing at least one fluid or gaseous tracer and being defined by a reservoir wall having a tracer-permeable reservoir wall portion (4) and a detection cavity (1) defined by a detection cavity wall having a tracer-permeable detection cavity wall portion (4), said tracer-permeable wall portions of the reservoir wall and the detection cavity wall, respectively, communicating with the surroundings (Fig. 2), the reservoir and the detection cavity are mutually interspaced elongated cavities (Fig. 2).

   Claim 1 differs from D1 in that the tracer-permeable reservoir wall portion and the tracer-permeable detection cavity wall portion are elongated side wall portions.

   The problem to be solved by this arrangement is to provide a sensor which is able to integrate measurements of tissue perfusion over an extended region of tissue.

   In D1 and other available prior art documents the tissue-permeable membrane forms the distal end of the sensor, so that the perfusion measurements can only be carried out for a single point or a limited space. No indication can be found in the prior art to provide tracer-permeable elongated side wall portions in order to solve the problem posed. Accordingly, the combination of features of claim 1 is neither known from, nor rendered obvious by, the available prior art. The requirements of Article 33(2)-(4) are met.

2. Claims 2-10 are dependent on claim 1 and therefore also meet the requirements of Article 33(2)-(4) PCT.

3. According to Rule 6.3(b) PCT all the features known in combination from D1 (see paragraph V 1. above) should have been placed in the preamble of claim 1.

SENSOR FOR MEASURING TISSUE PERFUSION

TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to devices for measurements of tissue perfusion according to the preamble of independent claim 1 and more particularly to a sensor for measurement of tissue perfusion over a given variable region and having a short response time.

BACKGROUND ART

Tissue perfusion is a measure of the amount (volume) of blood passing through a unit quantity of the tissue and is often measured with the unit ml blood/100 g tissue. Since all blood tissues are at the same time being supplied with nutrients and excrete waste products through diffusion between tissue cells and the blood, tissue perfusion is a very important factor indicating the state of health of a tissue. A method for the measurement of tissue perfusion is therefore highly pertinent, for instance for monitoring tissue during and after surgical operations and transplantations. Monitoring of potentially threatened tissue, e.g. muscular tissue, whose blood supply may become adversely affected by increasing pressure in the connective tissue membrane of the muscle, would be highly pertinent as an indication of when a pressure relieving operation should be initiated. Likewise monitoring of internal perfusion caused by the formation of oedemas in a heart stopped during operation could provide valuable information about the need of external supply of nutrients to the tissue of the heart. Within medical research, perfusion is an important parameter too.

A number of methods for determination of tissue perfusion are known. A technique consisting of an injection into the relevant tissue of radioactive xenon as a tracer and measuring the decay of radioactivity as a function of time has been described (see Larsen et al., 1966. Blood Flow through Human Adipose Tissue Determined

with Radioactive Xenon. Acta physiol. scand. 66, pp 337-345), but this technique suffers from a number of drawbacks in that its temporal resolution only amounts to approximately half an hour which is insufficient in many situations. Furthermore the location of the injection of the radioactive matter into the tissue relative to the location where the radioactivity is being measured is not particularly well-defined and finally, the application of radioactive matter per se involves potential hazards.

Another method of measuring tissue perfusion utilises continuous injection of ethanol during microdialysis. During microdialysis a fluid is being pumped very slowly through a fibre inserted into the tissue of the patient. The concentration of the fluid is in equilibrium with the surrounding tissue as the catheter is diffusion-open and the fluid is being collected via a return fibre. This method also suffers from an insufficient temporal resolution.

WO 97/46853 discloses a method and a microsensor which is able to measure tissue perfusion. The sensor comprises a tracer-permeable insert placed in a mouth of a tracer reservoir confined by a container, whereby said insert forms a permeable wall portion of the reservoir. A sensoric tip of a transducer is placed inside the insert or immediately outside of the latter. From the specification as a whole it appears that the tip of the transducer is very small, a diameter of 2 μm being mentioned. Consequently the transducer detects or measures the tracer concentration or pressure in a single point or in an extremely limited area. This also applies, if the transducer is provided with an inner cylindrical cavity, which is closed by the permeable insert or by a separate membrane forming the end wall of the transducer.

In connection with monitoring tissue perfusion for instance during surgical operations, the above-mentioned prior art suffers from the drawbacks of either insufficient temporal resolution or a very limited measurement space.

DISCLOSURE OF THE INVENTION

In order to circumvent the drawbacks and limitations of methods and devices for the measurement of tissue perfusion of prior art as mentioned above, it is the object of the present invention to provide a device (sensor) for the measurement of tissue perfusion which is able to integrate measurements of tissue perfusion over a larger

region in the tissue, the dimensions of which region can be varied as desired.

It is a further object of the present invention to provide a device with a response time not exceeding a few minutes.

It is a further object of the present invention to provide at least one embodiment of the general inventive idea which makes it possible to carry out non-invasive measurements of skin perfusion or measurements of prefusion in the surface layers of an organ, for instance for assessment of insufficient blood circulation.

These objects are accomplished with a device (sensor) according to the characterising clause of claim 1.

Various advantageous embodiments of the invention are defined in the dependent claims.

In the sensor for tissue perfusion according to the invention a fluid or gaseous tracer from a suitable supply means is supplied to a reservoir in which a constant high concentration of the tracer is maintained through diffusion from the supply means and from which reservoir a small portion of the tracer molecules will diffuse into a tracer-permeable barrier which is partly in contact with the surrounding tissue. From this barrier, part of the tracer molecules will move out into the surrounding tissue via a first spatially extended area, whereas another portion of the tracer molecules will move into an adjoining detector cavity via a second spatially extended area, said detector cavity being in communication with a suitable detector apparatus measuring the concentration of tracer in the detection cavity. The movement of tracer molecules from the reservoir into the surrounding tissue thus takes place via a tracer-permeable barrier which is in contact with the surrounding tissue via said first spatially extended area and the portion of the tracer molecules moving into the detection cavity arrives at the detection cavity via a tracer-permeable barrier and said second spatially extended area. Said first area thus constitutes the area of contact between said tracer-permeable barrier and the surrounding tissue, whose perfusion is to be measured, whereas said second area constitutes the area through which tracer molecules are able to reach the detection cavity. The distribution between the diffusion to the surrounding tissue and the diffusion to the detection cavity will be determined by the flow of dissolve matter in the surrounding tissue, i.e. the

perfusion, such that if the transport in the tissue is of large magnitude only a small portion of the tracer will diffuse into the detection cavity and vice versa. The signal from the detection apparatus will thus become a measure of tissue perfusion in the region surrounding the fibre.

According to the present invention the dimensions of the contact region between said tracer-permeable barrier and the surrounding tissue can be varied and thereby the region over which the tissue perfusion measurement is being carried out. It is also possible to vary the second area providing access to the detection cavity. By varying the geometry of the sensor, i.e. the relative layout of the reservoir, barrier and detection cavity, it is possible to vary the sensitivity and the radial resolution of the measurements being performed. It is furthermore possible to utilise a mixture of at least two tracers which might be supplied and removed substantially momentarily. A time-based measurement after instantaneous supply/removal to/from the tracer reservoir of two tracers with different diffusion coefficients will make it possible to distinguish between how much of the diffusion of the tracers away from the tracer reservoir is due to the concentration gradient within the tissue and how much is due to the transportation of the tracers away from the tissue by the blood. Thus, independent measures of perfusion and of diffusion coefficients within the tissue can be obtained.

It is furthermore possible to carry out measurements of O_2 and CO_2 and other gasses present in the tissue simultaneously with tissue perfusion.

As a suitable tracer for tissue perfusion measurements for instance helium, argon or hydrogen could be used, but it would also be possible to use other tracers.

Finally for in-situ calibration purposes the patient can inhale a gas which is being detected by the sensor placed in the tissue.

CLAIMS

1. Sensor for the measurement of tissue perfusion comprising a reservoir (4) for containing at least one fluid or gaseous tracer and being defined by a reservoir wall having a tracer-permeable reservoir wall portion, and a detection cavity (5) defined by a detection cavity wall having a tracer-permeable detection cavity wall portion, said tracer-permeable wall portions of the reservoir wall and the detection cavity wall, respectively, communicating with the surroundings, characterised in that the reservoir (4) and the detection cavity (5) are mutually interspaced, elongated cavities and that the tracer-permeable reservoir wall portion (3; 14') and the tracer-permeable detection cavity wall portions (3; 15') are elongated side wall portions.

2. Sensor according to claim 1, characterised in that the reservoir (4) and the detection cavity (5) are cylindrical and arranged in parallel.

3. Sensor according to claim 1 or 2, characterised in that the tracer-permeable wall portion (14') of the reservoir (4) and the tracer-permeable wall portion (15') of the detection cavity (5) are separate, mutually interspaced wall portions.

4. Sensor according to claim 3, characterised in that the reservoir (4) and the detection cavity (5) are separated by a tracer-impermeable barrier (19).

5. Sensor according to claim 3, characterised in that the reservoir (4) is defined by a tracer-permeable, tubular body (14) and that the detection cavity (5) is defined by a tracer-permeable, tubular body (15), and further that two bodies (14, 15) are interconnected by means of the tracer-impermeable barrier (19).

6. Sensor according to claim 1 or 2, characterised in that the tracer-permeable wall portion of the reservoir (4) and the tracer-permeable wall portion of the detection cavity (5) both are formed by a common tracer-permeable barrier (3) made from a tracer-permeable material, said tracer-permeable barrier (3) having a first longitudinally extending surface (18) being in contact with the surroundings, a second longitudinally extending surface (13) defining a portion of the detection cavity (5) and a third longitudinally extending surface (12) defining a portion of the tracer reservoir (4).

7. Sensor according to claim 6, characterised in that the tracer reservoir (4) is partly defined by a substantially U-shaped profile member (1), and that the detection cavity (5) is partly defined by a substantially U-shaped profile member (2) and further that the tracer-permeable barrier (3) sealingly engages the U-shaped profile members (1, 2) so as to close open sides (12, 13) thereof.

8. Sensor according to any of the claims 1 - 7, characterised in that the tracer-permeable reservoir wall portion (3; 14') and the tracer-permeable detection cavity wall portion (3; 15') extend substantially over the entire length of the sensor.

9. Sensor according to any of the claims 1-8, characterised in that the sensor is substantially symmetrical about a longitudinal plane (11).

10. Sensor according to any of the claims 1-9, characterised in that it comprises a series of reservoirs (4) and detection cavities (5) placed in side-by-side relationship.

Chas. Hude
Patents · Trade Marks · Designs

PATENTS
Tage Nørgaard °
Ulrik Nørgaard °
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Christian Kragelund ° □
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Kristiane B. Vandborg
Inge Petersen *renewals*
Sonja Nielsen *assignments*

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European Patent Office
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B R D

1 October 2001

Dear Sirs

PCT patent application No PCT/DK99/00522
Applicant: DAMGAARD, Lars, Riis et al.
My ref: 72790 UvF/Jen/cor

In response to the Written Opinion of 14 August 2001 I am pleased to forward new pages 11 and 12 containing a new set of claims in replacement of the former pages 11,12 and 13. Substitute pages 1- 4 containing a new introduction to the specification adapted to the amended claims as well as a mention of D1. The amendments in the specification further appear from the enclosed handwritten draft. No new subject-matter has been introduced by the amendments carried out.

The new claim 1 is based on D1 (WO 97/46853) as the closest related prior art.

WO 97/46853 discloses a sensor according to the preamble of the new claim 1, in which a tracer-permeable membrane or insert (4) is placed in the mouth (3) of a tracer reservoir confined by a container (2a), whereby the said insert forms a permeable wall portion of the reservoir. Further a sensoric tip (6) of a transducer (1) is placed inside the permeable insert (4). According to page 9, lines 15-17, the transducer may also be placed outside the insert (4).

In relation to the transducer and the sensoric tip thereof a number of examples of possible transducers are mentioned on page 6, lines 10-13. According to page 9, lines 10-11, the diameter of the tip of the transducer is 2 μm. From this information combined with the specification as a whole it appears that the transducer (1) detects or measures the tracer concentration or pressure in a single point or in an extremely limited space. This would also apply,

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Tax I.D./VAT No.: DK 12938179

if the transducer is provided with an inner cavity sealed by the permeable insert (4), when the tip (6) is inserted therein or by a separate membrane, when the tip (6) is placed outside of the insert (4). Further in the mentioned instances the insert (4) or the separate membrane would form an end wall of the transducer cavity.

The sensor according to the present invention is characterised in that the reservoir 4 and the detection cavity 5 are mutually interspaced, elongated cavities and that the tracer-permeable reservoir wall portion (3; 14') and the tracer-permeable detection cavity wall portions (3; 15') are elongated side wall portions.

Due to the elongated shape of the reservoir (4) and the detection cavity (5), respectively, and especially the elongated tracer-permeable wall portions of the reservoir wall (4) and the detection cavity (5), respectively, the diffusion of the tracer out of the reservoir (4) and the diffusion of the tracer into the detection cavity (5) and into the surrounding tissue during use of the sensor take place through considerably larger areas than when using a sensor according to the prior art.

As a result, it is possible to measure the tissue perfusion over a larger area of the tissue or to obtain measurement of an average tissue perfusion in said area of the tissue.

The Examining Authority is hereby respectfully requested to issue a Preliminary Examination report recognising the patentability of the present invention.

Yours faithfully

Ulrik von Freiesleben
Representative of the applicant

Add.Enc: FORM 1038

SENSOR FOR MEASURING TISSUE PERFUSION

TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to methods and devices for measurements of tissue perfusion according to the preamble of independent claims 1 and 7 and more particularly to a method and a sensor for measurement of tissue perfusion over a given variable region and having a short response time.

BACKGROUND ART

Tissue perfusion is a measure of the amount (volume) of blood passing through a unit quantity of the tissue and is often measured with the unit ml blood/100 g tissue. Since all blood tissue are at the same time being supplied with nutrients and excrete waste products through diffusion between tissue cells and the blood, tissue perfusion is a very important factor indicating the state of health of a tissue. A method for the measurement of tissue perfusion is therefore highly pertinent, for instance for monitoring tissue during and after surgical operations and transplantations. Monitoring of potentially threatened tissue, e.g. muscular tissue, whose blood supply may become adversely affected by increasing pressure in the connective tissue membrane of the muscle, would be highly pertinent as an indication of when a pressure relieving operation should be initiated. Likewise monitoring of internal perfusion caused by the formation of oedemas in a heart stopped during operation could provide valuable information about the need of external supply of nutrients to the tissue of the heart. Within medical research, perfusion is an important parameter too.

A number of methods for determination of tissue perfusion are known. A technique consisting of an injection into the relevant tissue of radioactive xenon as a tracer and measuring the decay of radioactivity as a function of time has been described (see Larsen et al., 1966. Blood Flow through Human Adipose Tissue Determined

with Radioactive Xenon. Acta physiol. scand. 66, pp 337-345), but this technique suffers from a number of drawbacks in that its temporal resolution only amounts to approximately half an hour which is insufficient in many situations. Furthermore the location of the injection of the radioactive matter into the tissue relative to the location where the radioactivity is being measured is not particularly well-defined and finally, the application of radioactive matter per se involves potential hazards.

Another method of measuring tissue perfusion utilises continuous injection of ethanol during microdialysis. During microdialysis a fluid is being pumped very slowly through a fibre inserted into the tissue of the patient. The concentration of the fluid is in equilibrium with the surrounding tissue as the catheter is diffusion-open and the fluid is being collected via a return fibre. This method also suffers from an insufficient temporal resolution.

WO 97/46853 discloses a method and a microsensor which is able to measure tissue perfusion, but measurements are limited to a very narrow space, and any heterogeneities of the tissue will thus make measurements of average perfusion more complicated.

In connection with monitoring tissue perfusion for instance during surgical operations, the above-mentioned prior art suffers from the drawbacks of either insufficient temporal resolution or a very limited measurement space.

DISCLOSURE OF THE INVENTION

In order to circumvent the drawbacks and limitations of methods and devices for the measurement of tissue perfusion of prior art as mentioned above, it is the object of the present invention to provide a method and a device (sensor) for the measurement of tissue perfusion which is able to integrate measurements of tissue perfusion over a larger region in the tissue, the dimensions of which region can be varied as desired.

It is a further object of the present invention to provide a method and a device with a response time not exceeding a few minutes.

It is a further object of the present invention to provide at least one embodiment of the general inventive idea which makes it possible to carry out non-invasive measurements of skin perfusion or measurements of prefusion in the surface layers of an organ, for instance for assessment of insufficient blood circulation.

These objects are accomplished with a method according to the characterising clause of claim 1 and a device (sensor) according to the characterising clause of claim 7.

Various advantageous embodiments of the invention are defined in the dependent claims.

In the method and sensor for tissue perfusion according to the invention a fluid or gaseous tracer from a suitable supply means is supplied to a reservoir in which a constant high concentration of the tracer is maintained through diffusion from the supply means and from which reservoir a small portion of the tracer molecules will diffuse into a tracer-permeable barrier which is partly in contact with the surrounding tissue. From this barrier, part of the tracer molecules will move out into the surrounding tissue via a first spatially extended area, whereas another portion of the tracer molecules will move into an adjoining detector cavity via a second spatially extended area, said detector cavity being in communication with a suitable detector apparatus measuring the concentration of tracer in the detection cavity. The movement of tracer molecules from the reservoir into the surrounding tissue thus takes place via a tracer-permeable barrier which is in contact with the surrounding tissue via said first spatially extended area and the portion of the tracer molecules moving into the detection cavity arrives at the detection cavity via a tracer-permeable barrier and said second spatially extended area. Said first area thus constitutes the area of contact between said tracer-permeable barrier and the surrounding tissue, whose perfusion is to be measured, whereas said second area constitutes the area through which tracer molecules are able to reach the detection

cavity. The distribution between the diffusion to the surrounding tissue and the diffusion to the detection cavity will be determined by the flow of dissolved matter in the surrounding tissue, i.e. the perfusion, such that if the transport in the tissue is of large magnitude only a small portion of the tracer will diffuse into the detection cavity and vice versa. The signal from the detection apparatus will thus become a measure of tissue perfusion in the region surrounding the fibre.

According to the present invention the dimensions of the contact region between said tracer-permeable barrier (100) and the surrounding tissue can be varied and thereby the region over which the tissue perfusion measurement is being carried out. It is also possible to vary the second area providing access to the detection cavity. By varying the geometry of the sensor, i.e. the relative layout of the reservoir, barrier and detection cavity, it is possible to vary the sensitivity and the radial resolution of the measurements being performed. It is furthermore possible to utilise a mixture of at least two tracers which might be supplied and removed substantially momentarily. A time-based measurement after instantaneous supply/removal to/from the tracer reservoir of two tracers with different diffusion coefficients will make it possible to distinguish between how much of the diffusion of the tracers away from the tracer reservoir is due to the concentration gradient within the tissue and how much is due to the transportation of the tracers away from the tissue by the blood. Thus, independent measures of perfusion and of diffusion coefficients within the tissue can be obtained.

According to the invention it is furthermore possible to carry out measurements of O_2 and CO_2 and other gasses present in the tissue simultaneously with tissue perfusion.

As a suitable tracer for tissue perfusion measurements for instance helium, argon or hydrogen could be used, but it would also be possible to use other tracers.

Finally for in-situ calibration purposes the patient can inhale a gas which is being detected by the sensor placed in the tissue.

CLAIMS

1. Method for the measurement of tissue perfusion where a fluid or gaseous tracer is being supplied from a tracer source via a reservoir (4) to the tissue, the perfusion of which is to be measured and detected by a detection device via a detection cavity (5), characterised in that the supply of tracer from said reservoir (4) to the surrounding tissue takes place via a spatially extended first area; that a part of the tracer molecules leaving said reservoir (4) diffuses to said detection cavity (5) via a spatially extended second area; and that said tissue perfusion is measured as a spatial average value dependent on the size and shape of said first and second areas with the aid of said detection device determining the amount of tracer diffusing into said detection cavity (5).

2. Method according to claim 1, characterised in that the size and shape of said spatially extended areas can be varied according to the individual application.

3. Method according to claim 1, characterised in that the response time of said method is less than 1 minute.

4. Method according to claim 1, characterised in that at least two tracers are used.

5. Method according to claim 1, characterised in that the tracer is helium.

6. Method according to claim 1, characterised in that O_2 and CO_2 are being measured simultaneously with tissue perfusion.

7. Sensor for the measurement of tissue perfusion according to claim 1, where a fluid or gaseous tracer is being supplied from a tracer source via a reservoir (4) to the tissue, the perfusion of which is to be measured, and detected by a detection device via a detection cavity (5), characterised in that said sensor comprises:
- first means such that the supply of tracer from said reservoir (4) to the surrounding tissue takes place via a spatially extended first area (14', 18); and

- second means such that a part of the tracer molecules leaving said reservoir (4) can arrive at said detection cavity (5) via a spatially extended second area (13, 15').

8. Sensor according to claim 7, characterised in that said first means comprises a tracer-permeable barrier (3, 14), the dimensions of which can be varied and that said second means comprises a tracer-permeable barrier (3,15), the dimensions of which can be varied, such that said variations of said dimensions results in variations of the size and shape of said spatially extended first and second areas according to the individual application.

9. Sensor according to claim 8, characterised in that said reservoir (4) communicates partly with said surrounding tissue through a spatially extended tracer-permeable barrier (3), having a first surface (18) which forms said first area, and partly with said detection cavity (5) through the same spatially extended tracer-permeable barrier (3), having a second surface (13) which forms said second area.

10. Sensor according to claim 8, characterised in that said reservoir (4) communicates with said surrounding tissue through a spatially extended tracer-permeable barrier (14), a first surface (14') of which forms said first area, and partly with said detection cavity (5) via said tissue and through another spatially extended tracer-permeable barrier (15), a second surface (15') of which forms said second area.

11. Sensor according to claim 8, characterised in that said reservoir (4) and said detection cavity (5) are separated by a barrier (3, 19), and that the reservoir (4), barrier (3, 19) and cavity (5) are built together to form a longitudinal sensor.

12. Sensor according to any of the claims 7 to 10, characterised in that said reservoir (4), said detection cavity (5) and said spatially extended tracer-permeable barriers (3, 14, 15) are helically wound around the longitudinal axis (11) of said sensor.

13. Sensor according to any of the claims 7 to 11, characterised in that said reservoir (4), said detection cavity (5) and said spatially extended tracer-permeable

barriers (3, 14, 15) are located between one of the large surfaces of a tracer-impermeable panel or disc (17) and the surface (20) of the skin or organ of a patient, the perfusion of the surface layers of which skin or organ is to be measured, and with said longitudinal axis 11 extending substantially parallel with said large surface of the panel or disc (17), such that said spatially extended tracer-permeable barriers (3, 14, 15) are partly in contact with the surface of the skin or organ, and such that tracer can move from said reservoir (4) into said skin or organ and either from here into said detection cavity (5), or directly from said reservoir (4) into said detection cavity (5).

14. Sensor according to any of the claims 7 to 11, characterised in that a series of said reservoir (4), said detection cavity (5) and said tracer-permeable barriers (3, 14, 15) are placed in side-by-side relationship with each other to cover a larger area of tissue.

15. Sensor according to claim 14, characterised in that said series of reservoirs (4), detection cavities (5) and tracer-permeable barriers (3, 14, 15) are located along one of the large sides of said panel or disc (17), such that they cover a substantial part of said side, and such that parts of said tracer-permeable barriers (3, 14, 15) can be brought into contact with the surface of the skin or organ of the patient.

16. Sensor according to claims 13 or 15, characterised in that said panel or disc (17) on the side facing the surface (20) of the skin or organ is provided with a pattern of partially open channels which can be connected to a vacuum source.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

CHAS.HUDE A/S
H.C. Andersens Boulevard 38
DK-1780 Copenhagen V
DANEMARK

Sagstype: pct | J.nr.: 72790 | Ing.: UvF
14 JAN. 2002
AS 400: Ve | Til hvem: UvF

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*: 11.01.2002

Applicant's or agent's file reference
72790/UvF/Sp

IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK99/00522	04/10/1999	04/10/1999

Applicant
DAMGAARD, Lars, Riis et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
72790/UvF/Sp		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK99/00522	04/10/1999	04/10/1999
International Patent Classification (IPC) or national classification and IPC A61B5/0275		
Applicant DAMGAARD, Lars, Riis et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12/04/2001	11.01.2002
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Abraham, V Telephone No. +49 89 2399 7463

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK99/00522

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

5-10	as originally filed	
1-4	with telefax of	01/10/2001

Claims, No.:

1-10	with telefax of	01/10/2001

Drawings, sheets:

1/6-6/6	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-10
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations
   see separate sheet

Reference is made to the following document:
D1: WO 97 46853 A (UNISENSE) 11 December 1997

V

1. Document D1 which is considered to represent the most relevant prior art discloses the following features of claim 1:

   Sensor for the measurement of tissue perfusion (Fig. 2) comprising a reservoir (2) for containing at least one fluid or gaseous tracer and being defined by a reservoir wall having a tracer-permeable reservoir wall portion (4) and a detection cavity (1) defined by a detection cavity wall having a tracer-permeable detection cavity wall portion (4), said tracer-permeable wall portions of the reservoir wall and the detection cavity wall, respectively, communicating with the surroundings (Fig. 2), the reservoir and the detection cavity are mutually interspaced elongated cavities (Fig. 2).

   Claim 1 differs from D1 in that the tracer-permeable reservoir wall portion and the tracer-permeable detection cavity wall portion are elongated side wall portions.

   The problem to be solved by this arrangement is to provide a sensor which is able to integrate measurements of tissue perfusion over an extended region of tissue.

   In D1 and other available prior art documents the tissue-permeable membrane forms the distal end of the sensor, so that the perfusion measurements can only be carried out for a single point or a limited space. No indication can be found in the prior art to provide tracer-permeable elongated side wall portions in order to solve the problem posed. Accordingly, the combination of features of claim 1 is neither known from, nor rendered obvious by, the available prior art. The requirements of Article 33(2)-(4) are met.

2. Claims 2-10 are dependent on claim 1 and therefore also meet the requirements of Article 33(2)-(4) PCT.

3. According to Rule 6.3(b) PCT all the features known in combination from D1 (see paragraph V 1. above) should have been placed in the preamble of claim 1.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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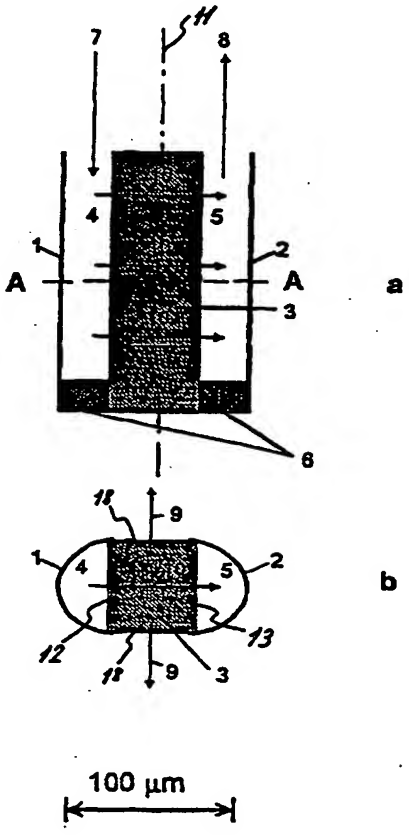
[Continued on next page]

(54) Title: SENSOR FOR MEASURING TISSUE PERFUSION



(57) Abstract: The invention relates to a method and a sensor for measurement of tissue perfusion. The sensor is provided with a reservoir (4) for a fluid or gaseous tracer and a tracer-permeable barrier (3), a sub-surface of which is in contact with the surrounding tissue and another sub-surface of which is in contact with a detection cavity (5) which is connected to a suitable apparatus for the measurement of tracer concentration in the detection cavity. The concentration of the tracer in the detection cavity is a measure of perfusion in the surrounding tissue. According to another embodiment of the invention it is also possible to carry out measurements of perfusion in the surface layers of the skin or of an organ.

WO 01/24692 A1

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

SENSOR FOR MEASURING TISSUE PERFUSION

TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to methods and devices for measurements of tissue perfusion according to the preamble of independent claims 1 and 7 and more particularly to a method and a sensor for measurement of tissue perfusion over a given variable region and having a short response time.

BACKGROUND ART

Tissue perfusion is a measure of the amount (volume) of blood passing through a unit quantity of the tissue and is often measured with the unit ml blood/100 g tissue. Since all blood tissue are at the same time being supplied with nutrients and excrete waste products through diffusion between tissue cells and the blood, tissue perfusion is a very important factor indicating the state of health of a tissue. A method for the measurement of tissue perfusion is therefore highly pertinent, for instance for monitoring tissue during and after surgical operations and transplantations. Monitoring of potentially threatened tissue, e.g. muscular tissue, whose blood supply may become adversely affected by increasing pressure in the connective tissue membrane of the muscle, would be highly pertinent as an indication of when a pressure relieving operation should be initiated. Likewise monitoring of internal perfusion caused by the formation of oedemas in a heart stopped during operation could provide valuable information about the need of external supply of nutrients to the tissue of the heart. Within medical research, perfusion is an important parameter too.

A number of methods for determination of tissue perfusion are known. A technique consisting of an injection into the relevant tissue of radioactive xenon as a tracer and measuring the decay of radioactivity as a function of time has been described (see Larsen et al., 1966. Blood Flow through Human Adipose Tissue Determined

with Radioactive Xenon. Acta physiol. scand. 66, pp 337-345), but this technique suffers from a number of drawbacks in that its temporal resolution only amounts to approximately half an hour which is insufficient in many situations. Furthermore the location of the injection of the radioactive matter into the tissue relative to the location where the radioactivity is being measured is not particularly well-defined and finally, the application of radioactive matter per se involves potential hazards.

Another method of measuring tissue perfusion utilises continuous injection of ethanol during microdialysis. During microdialysis a fluid is being pumped very slowly through a fibre inserted into the tissue of the patient. The concentration of the fluid is in equilibrium with the surrounding tissue as the catheter is diffusion-open and the fluid is being collected via a return fibre. This method also suffers from an insufficient temporal resolution.

WO 97/46853 discloses a method and a microsensor which is able to measure tissue perfusion, but measurements are limited to a very narrow space, and any heterogeneities of the tissue will thus make measurements of average perfusion more complicated.

In connection with monitoring tissue perfusion for instance during surgical operations, the above-mentioned prior art suffers from the drawbacks of either insufficient temporal resolution or a very limited measurement space.

DISCLOSURE OF THE INVENTION

In order to circumvent the drawbacks and limitations of methods and devices for the measurement of tissue perfusion of prior art as mentioned above, it is the object of the present invention to provide a method and a device (sensor) for the measurement of tissue perfusion which is able to integrate measurements of tissue perfusion over a larger region in the tissue, the dimensions of which region can be varied as desired.

It is a further object of the present invention to provide a method and a device with a response time not exceeding a few minutes.

It is a further object of the present invention to provide at least one embodiment of the general inventive idea which makes it possible to carry out non-invasive measurements of skin perfusion or measurements of prefusion in the surface layers of an organ, for instance for assessment of insufficient blood circulation.

These objects are accomplished with a method according to the characterising clause of claim 1 and a device (sensor) according to the characterising clause of claim 7.

Various advantageous embodiments of the invention are defined in the dependent claims.

In the method and sensor for tissue perfusion according to the invention a fluid or gaseous tracer from a suitable supply means is supplied to a reservoir in which a constant high concentration of the tracer is maintained through diffusion from the supply means and from which reservoir a small portion of the tracer molecules will diffuse into a tracer-permeable barrier which is partly in contact with the surrounding tissue. From this barrier, part of the tracer molecules will move out into the surrounding tissue via a first spatially extended area, whereas another portion of the tracer molecules will move into an adjoining detector cavity via a second spatially extended area, said detector cavity being in communication with a suitable detector apparatus measuring the concentration of tracer in the detection cavity. The movement of tracer molecules from the reservoir into the surrounding tissue thus takes place via a tracer-permeable barrier which is in contact with the surrounding tissue via said first spatially extended area and the portion of the tracer molecules moving into the detection cavity arrives at the detection cavity via a tracer-permeable barrier and said second spatially extended area. Said first area thus constitutes the area of contact between said tracer-permeable barrier and the surrounding tissue, whose perfusion is to be measured, whereas said second area constitutes the area through which tracer molecules are able to reach the detection

cavity. The distribution between the diffusion to the surrounding tissue and the diffusion to the detection cavity will be determined by the flow of dissolved matter in the surrounding tissue, i.e. the perfusion, such that if the transport in the tissue is of large magnitude only a small portion of the tracer will diffuse into the detection cavity and vice versa. The signal from the detection apparatus will thus become a measure of tissue perfusion in the region surrounding the fibre.

According to the present invention the dimensions of the contact region between said tracer-permeable barrier and the surrounding tissue can be varied and thereby the region over which the tissue perfusion measurement is being carried out. It is also possible to vary the second area providing access to the detection cavity. By varying the geometry of the sensor, i.e. the relative layout of the reservoir, barrier and detection cavity, it is possible to vary the sensitivity and the radial resolution of the measurements being performed. It is furthermore possible to utilise a mixture of at least two tracers which might be supplied and removed substantially momentarily. A time-based measurement after instantaneous supply/removal to/from the tracer reservoir of two tracers with different diffusion coefficients will make it possible to distinguish between how much of the diffusion of the tracers away from the tracer reservoir is due to the concentration gradient within the tissue and how much is due to the transportation of the tracers away from the tissue by the blood. Thus, independent measures of perfusion and of diffusion coefficients within the tissue can be obtained.

According to the invention it is furthermore possible to carry out measurements of O_2 and CO_2 and other gasses present in the tissue simultaneously with tissue perfusion.

As a suitable tracer for tissue perfusion measurements for instance helium, argon or hydrogen could be used, but it would also be possible to use other tracers.

Finally for in-situ calibration purposes the patient can inhale a gas which is being detected by the sensor placed in the tissue.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will now be described by way of exemplifying embodiments hereof and with reference to the accompanying drawings in which

Figure 1a is a longitudinal section of a first embodiment of a sensor according to the present invention;

Figure 1b is a cross section along the line indicated by A-A in Figure 1a;

Figure 2a is a longitudinal section of a second embodiment of a sensor according to the present invention;

Figure 2b is a cross section along the line indicated by B-B in Figure 2a;

Figure 3a is a side elevation cross-sectional view of a first version of a fourth embodiment of the present invention;

Figure 3b is a side elevation cross-sectional view of a second version of a fourth embodiment of the present invention;

Figure 4a is a side elevation cross-sectional view of a first version of a fifth embodiment of the present invention comprising interlaced reservoir- and detection cavity sections;

Figure 4b is a side elevation cross-sectional view of a second version of a fifth embodiment of the present invention comprising interlaced reservoir- and detection cavity sections;

Figure 5 is the response of a microsensor according to the invention as a function of time for a sudden change of perfusion obtained in a specific experiment; and

Figure 6 is a calibration curve of the sensor, i.e. the signal from the sensor as a function of the velocity of water obtained in the same experiment as mentioned in connection with Figure 5.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the following detailed part of the present description a number of different embodiments of the present invention will be described with reference to the accompanying drawings, but it is understood that these embodiments only constitute examples of the general inventive idea, and that other embodiments may

be conceivable by a person skilled in the art.

The first embodiment of the sensor is shown in Figure 1a and Figure 1b. The sensor is substantially symmetrical about a vertical plane 11 and comprises two U-shaped profiles 1, 2, the reservoir profile 1 and the detection profile 2 made of a gas-impermeable material such as metal or a suitable plastic material. The open sides 12, 13 of these two profiles 1, 2 are both in sealing abutment with a barrier 3 disposed between the reservoir 4 and the detection cavity 5 and extending throughout the vertical length of the sensor. The barrier 3 is made from a gas-permeable material, such as silicon or Teflon, such that two cavities, the reservoir 4 and the detection cavity 5, are defined. At the distal end hereof both the reservoir 4 and the detection cavity 5 are closed by a gas-impermeable barrier 6. At its proximal end the reservoir 4 is provided with an open inlet 7 which via a tube (not shown) is in communication with a supply container (also not shown) containing a gaseous tracer (for instance helium). The outer walls of both the tube and the container are made from a gas-impermeable material. The detection cavity 5 is at its proximal end provided with an open outlet 8 which via a tube (not shown) is in communication with a detector apparatus (vacuum pump and mass spectrometer as it is well-known within the art). The tube between the outlet 8 and the detector apparatus is made from a gas-impermeable and pressure resistant material. The reservoir profile 4, the detection cavity profile 5 and the barriers 3, 6 will in the following be referred to as the fibre.

The fibre is designed to be positioned within the tissue of a patient whose perfusion in that part of the tissue is to be measured. The functional principle of the invention is that a constantly high concentration of the tracer is maintained in the reservoir 4, the concentration being maintained via diffusion from the supply container. A small portion of the molecules of the tracer will due to diffusion move from the reservoir 4 out into the gas-permeable barrier 3 and a portion hereof will move out into the surrounding tissue through a first area 18, as indicated by the arrows 9, while another portion will move into the detection cavity 5 through a second area 13, as indicated by the arrows 10, and eventually be detected by means of the detection apparatus. The distribution between the diffusion to the surrounding tissue and the

diffusion to the detection cavity 5 will be determined by the transport of dissolved matter in the surrounding tissue, such that if the transport in the tissue is of a large magnitude only a small portion of the tracer will diffuse into the detection cavity 5 and vice versa. The signal from the detection apparatus will thus become a measure of tissue perfusion in the region surrounding the fibre.

Figure 2a and Figure 2b show a second embodiment of the present invention. Throughout the following description of the second embodiment of the present invention, elements identical with elements of the first embodiment shown in Figure 1a and Figure 1b will be designated by the same reference numerals as on Figure 1a and Figure 1b. The second embodiment is also substantially symmetrical about a vertical plane 11 and comprises two tubes: the reservoir tube 14 defining the reservoir 4 and the detection tube 15 defining the detection cavity 5, both tubes being made from a semi-gas-impermeable material (plastics). These two tubes 14, 15 are separated from each other by a barrier 19 made from a gas-impermeable material, such as metal or plastics. At the distal end, both the reservoir 4 and the detection cavity 5 are closed by a gas-impermeable barrier 6. At its proximal end the reservoir tube 14 is provided with an open inlet 7 which via a tube with gas-impermeable wall (not shown) is in communication with a supply container constructed from a gas-impermeable material containing a gaseous tracer (for instance helium). The detection tube 5 is at its proximal end provided with an outlet 8 communicating via a pressure resistant tube with gas-impermeable wall with a detection apparatus (vacuum pump and mass spectrometer as it is well-known within the art). The reservoir tube 14, the detection tube 15 and the barriers 6, 19 will in the following be referred to as the fibre.

The fibre is designed to be positioned within the tissue of a patient whose perfusion in that part of the tissue is to be measured. The functional principle of the invention is that a constantly high concentration of the tracer is maintained in the reservoir 4, the concentration being maintained via diffusion from the supply container. A small portion of the molecules of the tracer will due to diffusion move from the reservoir 4 out through the wall of the reservoir tube 14 through a first area 14' (as delimited by the two arrows C in Figure 2b) and into the surrounding tissue, as indicated by the

arrows 9. Of this quantity of tracer, a portion will diffuse into the detection tube and pass through the wall (15) through a second area 15' (as delimited by the two arrows D in Figure 2b) to the detection cavity 5 as indicated by the arrows 16, from where it will be detected by the detection apparatus. The quantity reaching the detection cavity will depend on the transport conditions in the tissue through which diffusion takes place, and the signal from the detector will thus be a measure of the transport conditions, i.e. the perfusion, in the region around the fibre.

A third embodiment (not shown) of the present invention is directly derivable from the two first embodiments described above in that the structures shown in Figure 1 and Figure 2 are helically wound around the longitudinal axis 11 of the fibres. This has the effect of making the sensitivity of the fibres in a plane perpendicular to the longitudinal axis omnidirectional. A suitable pitch of the helix could for instance constitute 10 revolutions per cm.

Figure 3a and 3b show a fourth embodiment of the present invention which differs significantly from the three previous embodiments described above. Where the three above embodiments were designed to be inserted into the tissue, the fourth embodiment of the present invention is fastened non-invasively on the surface (20) of the skin or of an organ of a patient to provide the possibility of carrying out measurements of perfusion in the surface layers of the skin or the organ such as carried out for the assessment of insufficient blood circulation in for instance a leg of the patient.

The operational principle of the first version of the fourth embodiment shown in Figure 3a corresponds to the operational principle of the first embodiment shown in Figure 1a and Figure 1b. The operational principle of the second version of the fourth embodiment shown in Figure 3b corresponds to the operational principle of the second embodiment shown in Figure 2a and Figure 2b.

In the embodiment shown in Figure 3a, the inner side, i.e. the side facing the surface (20) of the skin or organ of the patient, of a gas-impermeable disc 17 is provided with a single one of the sensors according to the first embodiment of the

present invention shown in Figure 1a and Figure 1b. The longitudinal axis 11 of the sensor extends substantially parallel with the plane of said disc 17 and one of the sides 18 of the tracer-permeable barrier 3 is in contact with the surface (20) of the patient's skin or organ. Diffusion of tracer molecules from the barrier 3 into the skin or organ thus only takes place via this single side 18. The function of the disc 17 is to enable sufficient contact pressure between fibre and skin or organ and to prevent escape of tracer molecules in the direction opposite the skin or organ.

In the embodiment shown in Figure 3b the inner side, i.e. the side facing the surface (20) of the skin or organ of the patient, of a gas-impermeable disc 17 is provided with a single one of the sensors according to the second embodiment of the present invention shown in Figure 2a and Figure 2b. The longitudinal axis 11 of the sensor extends substantially parallel with the plane of said disc 17 and parts of the tracer-permeable walls 14 and 15 of the reservoir 4 and detection cavity 5, respectively, are in contact with the surface of the patient's skin or organ. The width w of the tracer-impermeable barrier is modified compared to the second embodiment in order to provide a contact area of sufficient size between the reservoir 4 and the surface of the skin or organ and between the detection cavity 5 and the skin or organ, respectively. Also the side of the reservoir 4 facing away from the detection cavity 5 and the side of the detection cavity 5 facing away from the reservoir 4 are covered with tracer-impermeable barriers 19.

A more preferable variation of the embodiments shown in Figure 3a and Figure 3b is shown in Figure 4a and Figure 4b. The difference between the embodiments shown in Figures 3a/3b and Figures 4a/4b is that both the reservoir 4 and the detection cavity 5 in the embodiments shown in Figure 4a and Figure 4b are split up into a plurality of substantially identical reservoir/detection cavity sub-systems covering a substantial part of the inner side of said gas-impermeable disc 17. The functional principles of the embodiments shown in Figure 4a and Figure 4b correspond to those described in connection with the preceding embodiments and will hence not be described in detail here.

In the embodiments of the present invention according to Figures 3a, 3b, 4a and 4b

it is possible to provide the inner side of the disc 17 with a system of partially open channels where the openings are in contact with the surface 20 of the patient's skin or organ, and where the channels can be connected to a suitable vacuum source. Application of vacuum to the channels ensures a firm attachment of the disc 17 to the skin or organ of the patient.

Figure 5 shows the response of the sensor in volts as a function of time obtained in an experiment where water moves through a sand-filled tube simulating a bloodflow through tissue. The velocity of the water changed suddenly from 4.8 micrometers/second to the left of the arrow in the Figure to 24.8 micrometers/second immediately to the right of the arrow. A response time of approximately 0.5 - 1.0 minutes is possible, although the response time varies as a function of perfusion, and increases when the velocity through the tissue changes from a relatively high level to a relatively low level and vice versa.

Figure 6 shows a calibration curve obtained in the same experiment as in Figure 5, i.e. a curve of the signal from the detection device in Volts as a function of the velocity of water in mm/second.

Above, a number of different embodiments of the present invention have been shown and described, but it is understood that these embodiments only constitute examples of the general inventive idea as defined in the accompanying claims, and that other embodiments of the present invention might be conceivable by a person skilled in the art.

CLAIMS

1. Method for the measurement of tissue perfusion where a fluid or gaseous tracer is being supplied from a tracer source via a reservoir (4) to the tissue, the perfusion of which is to be measured and detected by a detection device via a detection cavity (5), characterised in that the supply of tracer from said reservoir (4) to the surrounding tissue takes place via a spatially extended first area; that a part of the tracer molecules leaving said reservoir (4) diffuses to said detection cavity (5) via a spatially extended second area; and that said tissue perfusion is measured as a spatial average value dependent on the size and shape of said first and second areas with the aid of said detection device determining the amount of tracer diffusing into said detection cavity (5).

2. Method according to claim 1, characterised in that the size and shape of said spatially extended areas can be varied according to the individual application.

3. Method according to claim 1, characterised in that the response time of said method is less than 1 minute.

4. Method according to claim 1, characterised in that at least two tracers are used.

5. Method according to claim 1, characterised in that the tracer is helium.

6. Method according to claim 1, characterised in that O_2 and CO_2 are being measured simultaneously with tissue perfusion.

7. Sensor for the measurement of tissue perfusion according to claim 1, where a fluid or gaseous tracer is being supplied from a tracer source via a reservoir (4) to the tissue, the perfusion of which is to be measured, and detected by a detection device via a detection cavity (5), characterised in that said sensor comprises:
- first means such that the supply of tracer from said reservoir (4) to the surrounding tissue takes place via a spatially extended first area (14', 18); and

- second means such that a part of the tracer molecules leaving said reservoir (4) can arrive at said detection cavity (5) via a spatially extended second area (13, 15').

8. Sensor according to claim 7, characterised in that said first means comprises a tracer-permeable barrier (3, 14), the dimensions of which can be varied and that said second means comprises a tracer-permeable barrier (3,15), the dimensions of which can be varied, such that said variations of said dimensions results in variations of the size and shape of said spatially extended first and second areas according to the individual application.

9. Sensor according to claim 8, characterised in that said reservoir (4) communicates partly with said surrounding tissue through a spatially extended tracer-permeable barrier (3), having a first surface (18) which forms said first area, and partly with said detection cavity (5) through the same spatially extended tracer-permeable barrier (3), having a second surface (13) which forms said second area.

10. Sensor according to claim 8, characterised in that said reservoir (4) communicates with said surrounding tissue through a spatially extended tracer-permeable barrier (14), a first surface (14') of which forms said first area, and partly with said detection cavity (5) via said tissue and through another spatially extended tracer-permeable barrier (15), a second surface (15') of which forms said second area.

11. Sensor according to claim 8, characterised in that said reservoir (4) and said detection cavity (5) are separated by a barrier (3, 19), and that the reservoir (4), barrier (3, 19) and cavity (5) are built together to form a longitudinal sensor.

12. Sensor according to any of the claims 7 to 10, characterised in that said reservoir (4), said detection cavity (5) and said spatially extended tracer-permeable barriers (3, 14, 15) are helically wound around the longitudinal axis (11) of said sensor.

13. Sensor according to any of the claims 7 to 11, characterised in that said reservoir (4), said detection cavity (5) and said spatially extended tracer-permeable

barriers (3, 14, 15) are located between one of the large surfaces of a tracer-impermeable panel or disc (17) and the surface (20) of the skin or organ of a patient, the perfusion of the surface layers of which skin or organ is to be measured, and with said longitudinal axis 11 extending substantially parallel with said large surface of the panel or disc (17), such that said spatially extended tracer-permeable barriers (3, 14, 15) are partly in contact with the surface of the skin or organ, and such that tracer can move from said reservoir (4) into said skin or organ and either from here into said detection cavity (5), or directly from said reservoir (4) into said detection cavity (5).

14. Sensor according to any of the claims 7 to 11, characterised in that a series of said reservoir (4), said detection cavity (5) and said tracer-permeable barriers (3, 14, 15) are placed in side-by-side relationship with each other to cover a larger area of tissue.

15. Sensor according to claim 14, characterised in that said series of reservoirs (4), detection cavities (5) and tracer-permeable barriers (3, 14, 15) are located along one of the large sides of said panel or disc (17), such that they cover a substantial part of said side, and such that parts of said tracer-permeable barriers (3, 14, 15) can be brought into contact with the surface of the skin or organ of the patient.

16. Sensor according to claims 13 or 15, characterised in that said panel or disc (17) on the side facing the surface (20) of the skin or organ is provided with a pattern of partially open channels which can be connected to a vacuum source.

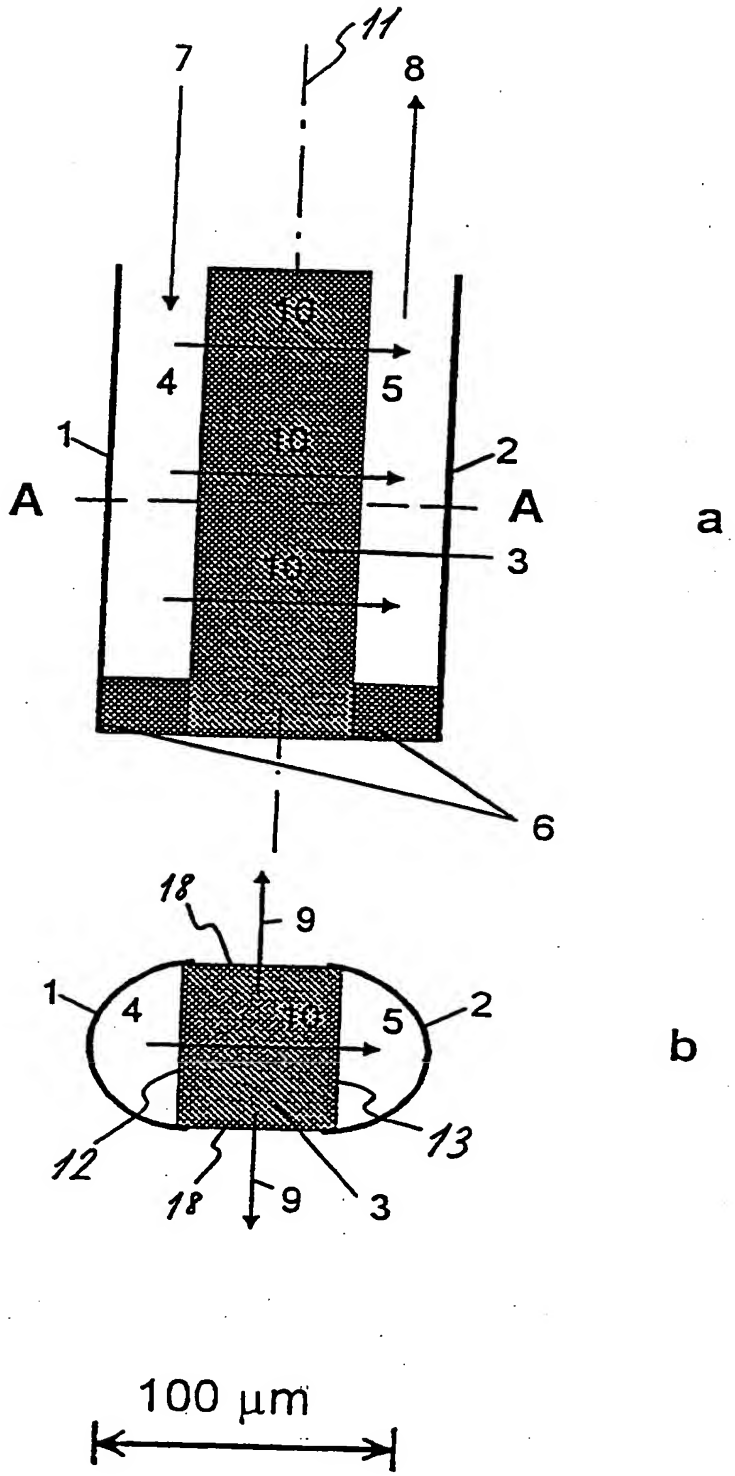


Fig. 1

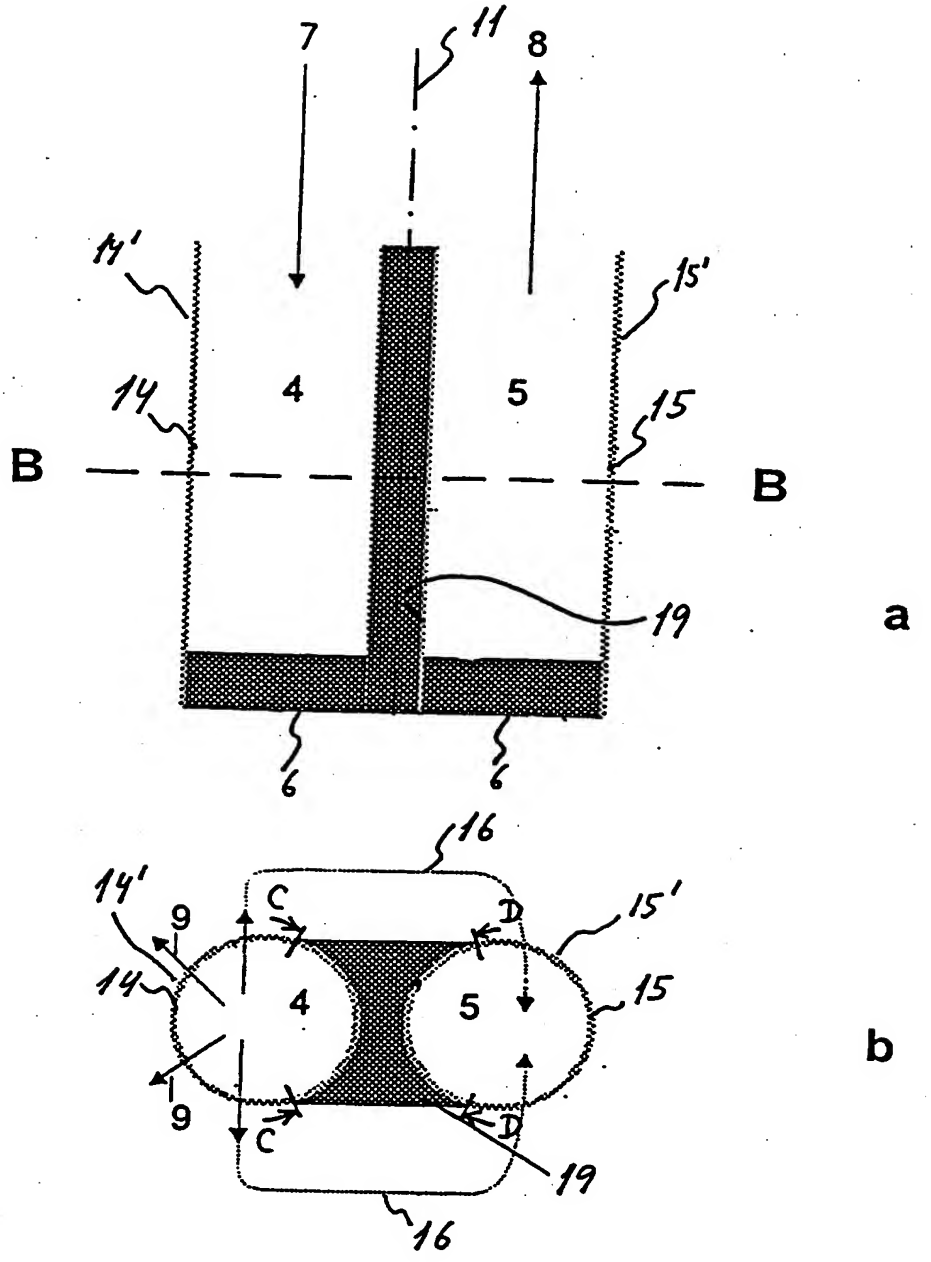


Fig. 2

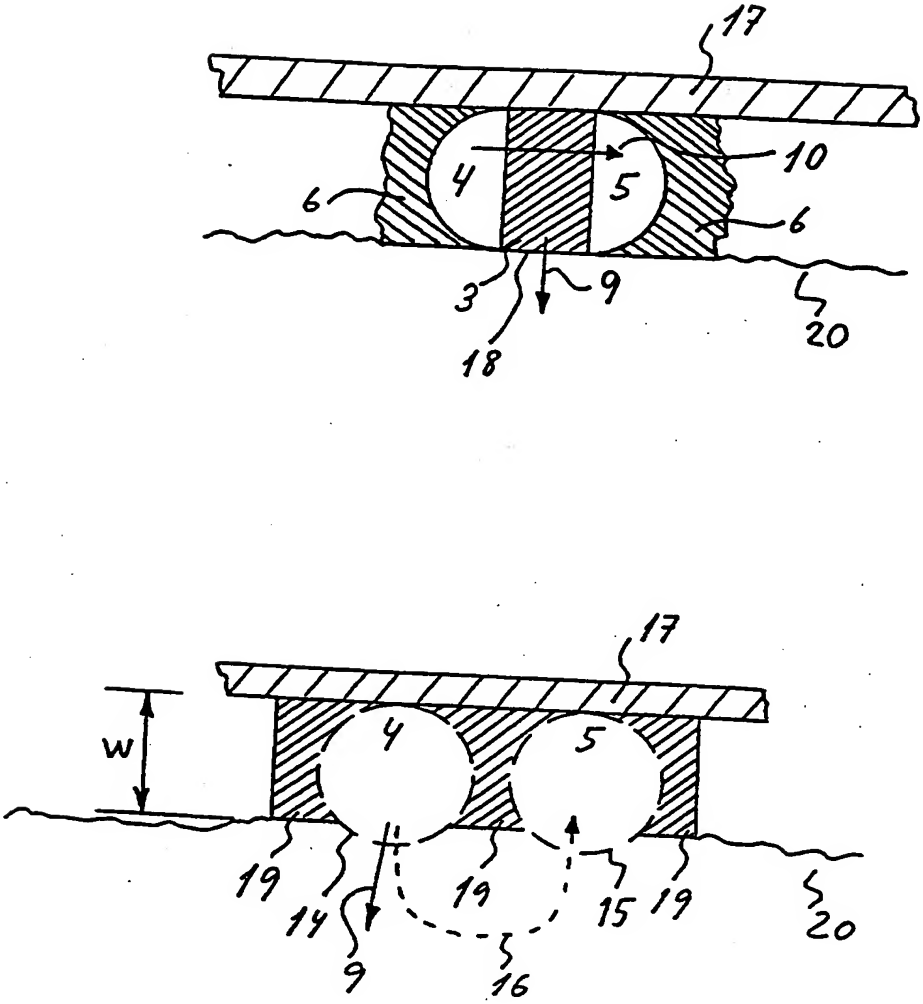
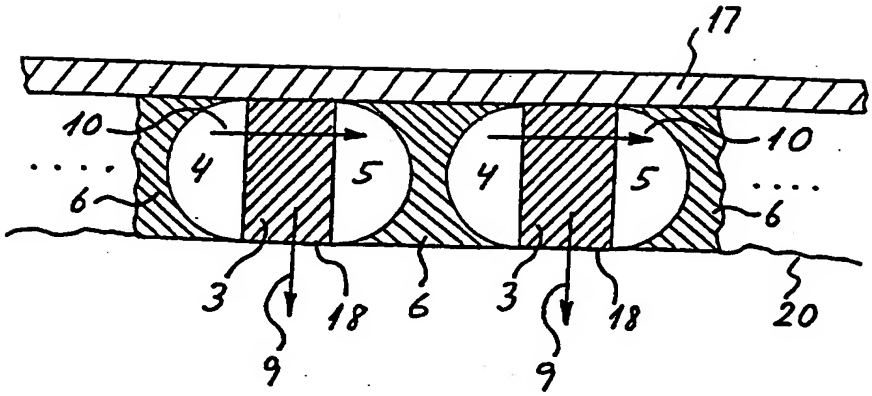


Fig. 3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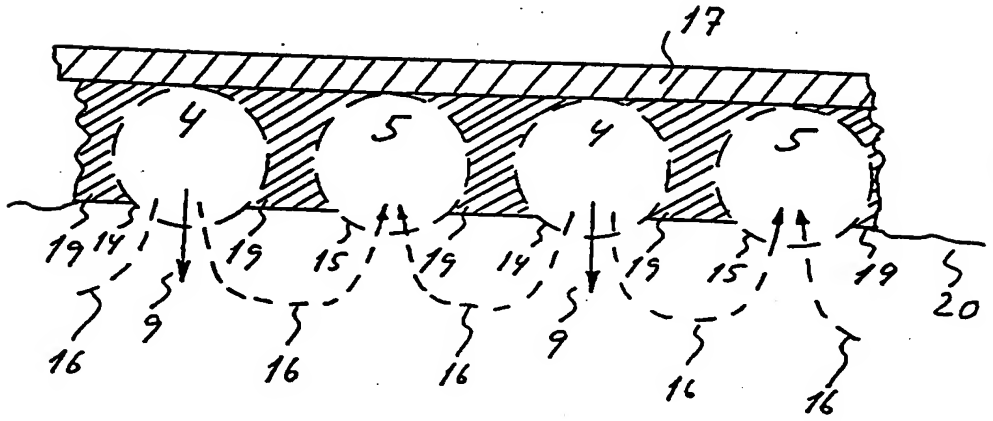
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b

Fig. 4

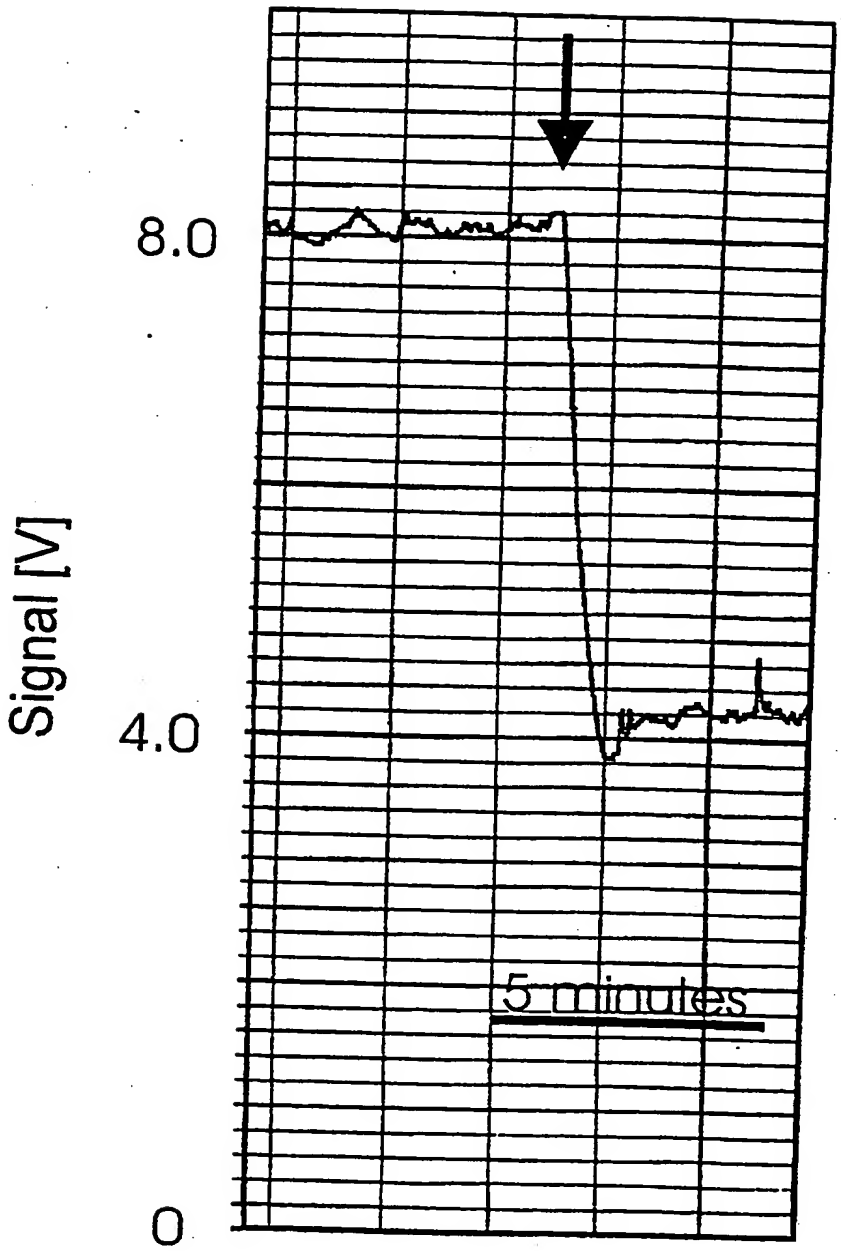

Fig. 5

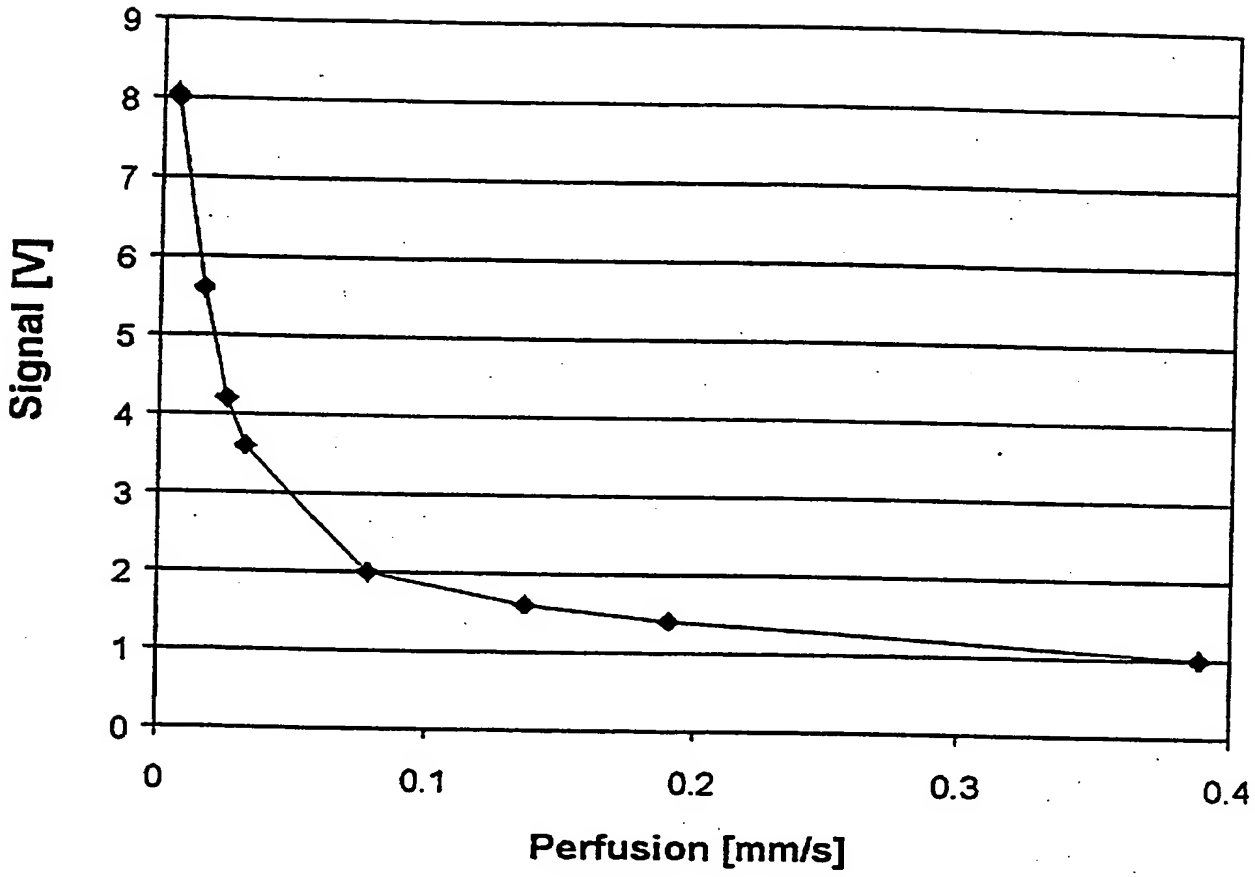

Fig. 6

INTERNATIONAL SEARCH REPORT

Intern. Application No
PCT/DK 99/00522

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B5/0275 G01F1/704

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61B G01N G01F G01P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 46853 A (UNISENSE) 11 December 1997 (1997-12-11) abstract; figures 1,2 page 4, line 2-14 page 7, line 20-30 page 8, line 35 -page 9, line 34	7,8
A	WO 97 19345 A (DAMGAARD LARS RIIS ;REVSBECH NIELS PETER) 29 May 1997 (1997-05-29) abstract; figure 1 page 4, line 15-19 page 6, line 17-27 page 7, line 24-31	7
A	WO 95 16392 A (MODERN TECHNOLOGIES CORP) 22 June 1995 (1995-06-22) abstract	7

-/—

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 May 2000	06/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Jonsson, P.O.

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 549 394 A (HEMODIA SOCIETE ANONYME) 30 June 1993 (1993-06-30) abstract; figure 1 column 3, line 23-35	7,8
A	US 5 594 179 A (MARSH LAWRENCE B) 14 January 1997 (1997-01-14) abstract; figure 1	7
A	EP 0 747 675 A (AIR LIQUIDE) 11 December 1996 (1996-12-11) abstract	7
A	WO 98 59240 A (AROMASCAN PLC) 30 December 1998 (1998-12-30) abstract; figure 2	14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00522

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inten[redacted] Application No
PCT/DK 99/00522

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9746853	A	11-12-1997	DK	63396 A	07-12-1997
			AU	3090597 A	05-01-1998
			EP	0902881 A	24-03-1999
WO 9719345	A	29-05-1997	AU	7621496 A	11-06-1997
			EP	0882225 A	09-12-1998
			JP	2000500580 T	18-01-2000
			US	6030828 A	29-02-2000
WO 9516392	A	22-06-1995	US	5439003 A	08-08-1995
			AU	690602 B	30-04-1998
			AU	1099195 A	03-07-1995
			BR	9408349 A	26-08-1997
			EP	0734225 A	02-10-1996
			US	5724982 A	10-03-1998
EP 0549394	A	30-06-1993	FR	2684864 A	18-06-1993
US 5594179	A	14-01-1997	NONE		
EP 0747675	A	11-12-1996	US	5672827 A	30-09-1997
			BR	9602672 A	06-10-1998
			CA	2178533 A	08-12-1996
			JP	9105656 A	22-04-1997
WO 9859240	A	30-12-1998	NONE		

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

CHAS.HUDE A/S
H.C. Andersens Boulevard 33
DK-1780 Copenhagen V
DANEMARK

Sagstype	J.nr.	Ing.
PA	72790	UVF
17 AUG 2001		
AS 400 SP	Til hvem UVF	

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	14.08.2001
Applicant's or agent's file reference: 72790/UvF/Sp	**REPLY DUE** **within 1 month(s) and 15 days** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK99/00522	04/10/1999	04/10/1999

International Patent Classification (IPC) or both national classification and IPC

A61B5/0275

Applicant

DAMGAARD, Lars, Riis et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☐	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 04/02/2002.

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner

Abraham, V

Formalities officer (incl. extension of time limits)
Edel, M
Telephone No. +49 89 2399 2426

I. Basis of the opinion

1. With regard to the **elements** of the international application (Replacement *sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

Description, pages:

1-10 as originally filed

Claims, No.:

1-16 as originally filed

Drawings, sheets:

1/6-6/6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-16,

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 7-16 are so unclear that no meaningful opinion could be formed (*specify*):
   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-6.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

Reference is made to the following document:
D1: WO 97 46853 A (UNISENSE) 11 December 1997

III

1. Claim 7 does not meet he requirements of Article 6 PCT, because the general formulations "**first means such that** the supply of tracer from said reservoir to the surrounding tissue takes place via a spatially extended first area" and "**second means such that** a part of the tracer molecules leaving said reservoir can arrive at said detection cavity via a spatially extended second area" used in this claim are entirely unclear. With these formulations the claim attempts to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added.

2. Furthermore, the features of the preamble of claim 7 relate to a method of using the apparatus rather than clearly defining the apparatus in terms of its technical features. The intended limitations are therefore not clear from this claim, contrary to the requirements of Article 6 PCT.

3. It is at present not possible to carry out a detailed examination of claims 7-16, because it is entirely unclear which features may define the sensor according to the present application.

4. Dependent claims 9-11 are also unclear (Article 6 PCT). These claims define "**a** spatially extended tracer-permeable barrier" (claims 9 and 10), "**another** partially extended tracer-permeable barrier" (claim 10) and "**a** barrier" (claim 11). However, these features have already been defined in claim 8 on which claims 9-11 are dependent.

5. As a consequence it appears that is under Article 6 PCT it not possible to define both embodiments of the present application in terms of a single independent claim. Furthermore, it is not clear whether the requirement of unity of invention (Rule 13.1 PCT) between both embodiments is met.

6. However, for the sake of accelerating the procedure, the following statements are

made:

6.1 A sensor according to the first embodiment appears to be known from document D1, which discloses the following:

Sensor for the measurement of tissue perfusion (Fig. 1) comprising:
a reservoir of a fluid or gaseous tracer (2),
a detection device comprising a detection cavity (1),
the reservoir comprises a tracer permeable barrier (4) having a first area (Fig. 2),
the detection cavity comprises a tracer permeable barrier (4) having a second area (Fig. 2).

6.2 D1 also discloses variable dimensions of the barrier (page 4, lines 16-18) and a longitudinal sensor (Fig. 2).

6.3 Fig. 2 of D1 shows all the features of the first embodiment of the present application defining one tracer permeable barrier (4) in contact with the tissue (5) and the detection chamber (1).

6.4 The second embodiment of the application shown in Figures 2a and 2b comprises two separate tracer permeable barriers defining separate locations for tracer infusion and tracer detection, so that the tracer concentration is measured directly inside the tissue. This appears to be the conventional approach for a perfusion sensor (see D1 page 8, lines 35-37). D1 also discloses a corresponding embodiment where the sensor is inserted through the barrier into the tissue in order to measure the tracer concentration directly inside the tissue (page 9, lines 15-17).

6.5 Accordingly, it appears that the subject-matter of claims 7-11 lacks novelty over D1 (Article 33(2) PCT).

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EP

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: 72790 UvF/Sp

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/DK99/00522	4 October 1999	

Title of invention: SENSOR FOR MEASURING TISSUE PERFUSION

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Lars Riis DAMGAARD,
Vesterbrogade 6B, st.tv
DK-8000 Århus C
Denmark

Telephone No.:

Facsimile No.:

Teleprinter No.:

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
Denmark	Denmark

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Jens Kristian GUNDERSEN,
Søskrænten 29
Dk-8260 Viby
Denmark

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
Denmark	Denmark

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Lars Hauer LARSEN,
Overdrevet 25
DK-8382 Hinnerup
Denmark

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
Denmark	Denmark

[X] Further applicants are indicated on a continuation sheet.

Sheet No. 2

International application No.
PCT/DK99/00522

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Thomas KJÆR
Sjælør Boulevard 89, st.tv.
DK-2500 Valby
Denmark

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
Denmark	Denmark

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on another continuation sheet.

International application No.
PCT/DK99/00522

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is [x] agent [ ] common representative

and [x] has been appointed earlier and represents the applicant(s) also for international preliminary examination.

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

CHAS.HUDE A/S
33, H.C. Andersens Boulevard
DK-1780 Copenhagen V
Denmark

Telephone No.: +45 33 15 45 14

Facsimile No.: +45 33 15 45 35

Teleprinter No.:

[ ] **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special addr ess to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination **to start on the basis of:**

[x] the international application as originally filed

the description [ ] as originally filed
[ ] as amended under Article 34

the claims [ ] as originally filed
[ ] as amended under Article 19 (together with any accompanying statement)
[ ] as amended under Article 34

the drawings [ ] as originally filed
[ ] as amended under Article 34

2. [ ] The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. [ ] The applicant wishes the start of the international preliminary examination **to be postponed** until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

[x] which is the language in which the international application was filed.
[ ] which is the language of a translation furnished for the purposes of international search.
[ ] which is the language of publication of the international application.
[ ] which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby **elects all eligible States** *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes **not to elect:**

Sheet No. 4.

International application No.
PCT/DK99/00522

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. [x] fee calculation sheet
2. [ ] separate signed power of attorney
3. [ ] copy of general power of attorney; reference number, if any:
4. [ ] statement explaining lack of signature
5. [ ] nucleotide and or amino acid sequence listing in computer readable form
6. [x] other *(specify)*: Search Report

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Chas.Hude A/S

Ulrik von Freiesleben
Representative of Applicant

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

kop● φko 9/4 ●

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

International application No.	PCT/DK99/00522
Applicant's or agent's file reference	72790 UvF/Sp

For International Preliminary Examining Authority use only

Date stamp of the IPEA

Applicant

DAMGAARD, Lars Riis et al.

Calculation of prescribed fees

1. Preliminary examination fee	1.533,- EUR	P
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)*	147,- EUR	H
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box.....	1.680,- EUR	TOTAL

Mode of Payment

[X]	authorization to charge deposit account with the IPEA (see below)	[ ]	cash
[ ]	cheque	[ ]	revenue stamps
[ ]	postal money order	[ ]	coupons
[ ]	bank draft	[ ]	other *(specify):*

Deposit Account Authorization *(this mode of payment may not be available at all IPEAs)*

The IPEA/ EP [X] is hereby authorized to charge the total fees indicated above to my deposit account.

[ ] *(this check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

28030014	9 April 2001	
Deposit Account Number	Date *(day/month/year)*	Signature

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
CHAS.HUDE A/S
H.C. Andersens Boulevard 33
DK-1780 Copenhagen V
DANEMARK

Sagstype | Jnr. | Ing.
PM | 72790 | Ltf
20 APR. 2001
AS 400 SP | Til hvem SP

Saj Kos SP

Date of mailing (day/month/year) 12 April 2001 (12.04.01)	
Applicant's or agent's file reference 60161/SGW/AW	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/DK99/00522	04 October 1999 (04.10.99)	

Applicant
DAMGAARD, Lars, Riis et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   12 April 2001 (12.04.01) under No. WO 01/24692

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a **demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

To:

CHAS.HUDE A/S
H.C. Andersens Boulevard 33
DK-1780 Copenhagen V
DENMARK

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

Sagstype PA J.nr. 72780 Ing.

Date of mailing (day/month/year) 13 June 2001 (13.06.01)	25 JUNI 2001
Applicant's or agent's file reference 60161/SGW/AW	UVF **IMPORTANT INFORMATION**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/DK99/00522	04 October 1999 (04.10.99)	

Applicant
DAMGAARD, Lars, Riis et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
   National :AU,BG,CA,CN,CZ,DE,IL,JP,KP,KR,MN,NO,NZ,PL,RO,RU,SE,SK,US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   AP :GH,GM,KE,LS,MW,SD,SL,SZ,TZ,UG,ZW
   EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
   OA :BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
   National :AE,AL,AM,AT,AZ,BA,BB,BR,BY,CH,CR,CU,DK,DM,EE,ES,FI,GB,GD,GE,GH, GM,HR,HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MW,MX,PT,SD,SG, SI,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW

3. The applicant is reminded that he must enter the "national phase" **before the expiration of 30 months from the priority date** before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed **until 31 months from the priority date** for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:
Odile ALIU

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

CHAS.HUDE A/S
H.C. Andersens Boulevard 33
DK-1780 Copenhagen V
DANEMARK

Date of mailing (day/month/year) 09 February 2001 (09.02.01)	
Applicant's or agent's file reference 60161/SGW/AW	**IMPORTANT NOTIFICATION**
International application No. PCT/DK99/00522	**International filing date** (day/month/year) 04 October 1999 (04.10.99)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
BUDDE, SCHOU & OSTENFELD A/S Vestergade 31 DK-1456 København K Denmark		
	Telephone No. +45 33 11 05 13	
	Facsimile No. +45 33 11 05 92	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☒ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address	State of Nationality	State of Residence
CHAS.HUDE A/S H.C. Andersens Boulevard 33 DK-1780 Copenhagen V Denmark		
	Telephone No. 45 33 15 45 14	
	Facsimile No. 45 33 15 45 35	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the International Preliminary Examining Authority
☐ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No.: (41-22) 740.14.35	Authorized officer S. Buttay Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

003828969

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 60161/SGW/AW

Box No. I TITLE OF INVENTION

SENSOR FOR MEASURING TISSUE PERFUSION

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

DAMGAARD, Lars Riis
Vesterbrogade 6B, st.tv.
DK-8000 Århus C
Denmark

95521

[X] This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: Denmark

State *(that is, country)* of residence: Denmark

This person is applicant for the purposes of: [X] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

GUNDERSEN, Jens Kristian
Søskrænten 29
DK-8260 Viby
Denmark

95522

This person is:

[ ] applicant only

[X] applicant and inventor

[ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: Denmark

State *(that is, country)* of residence: Denmark

This person is applicant for the purposes of: [X] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

[X] Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: [X] agent [ ] common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BUDDE, SCHOU & OSTENFELD A/S
Vestergade 31
DK-1456 København K
Denmark

Telephone No. +45 33 11 05 13

Facsimile No. +45 33 I1 05 92

Teleprinter No. 19796 budde dk

[ ] **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III **FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

LARSEN, Lars Hauer
Overdrevet 25
DK-8382 Hinnerup
Denmark

95523

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: Denmark

State *(that is, country)* of residence: Denmark

This person is applicant for the purposes of: ☒ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

KJÆR, Thomas
Sjælør Boulevard 89, st.tv.
DK-2500 Valby
Denmark

95524

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: Denmark

State *(that is, country)* of residence: Denmark

This person is applicant for the purposes of: ☒ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- ☒ AP **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP **European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☒ AE United Arab Emirates
- ☒ AL Albania
- ☒ AM Armenia
- ☒ AT Austria
- ☒ AU Australia
- ☒ AZ Azerbaijan
- ☒ BA Bosnia and Herzegovina
- ☒ BB Barbados
- ☒ BG Bulgaria
- ☒ BR Brazil
- ☒ BY Belarus
- ☒ CA Canada
- ☒ CH and LI Switzerland and Liechtenstein
- ☒ CN China
- ☒ CU Cuba
- ☒ CZ Czech Republic
- ☒ DE Germany
- ☒ DK Denmark
- ☒ EE Estonia
- ☒ ES Spain
- ☒ FI Finland
- ☒ GB United Kingdom
- ☒ GD Grenada
- ☒ GE Georgia
- ☒ GH Ghana
- ☒ GM Gambia
- ☒ HR Croatia
- ☒ HU Hungary
- ☒ ID Indonesia
- ☒ IL Israel
- ☒ IN India
- ☒ IS Iceland
- ☒ JP Japan
- ☒ KE Kenya
- ☒ KG Kyrgyzstan
- ☒ KP Democratic People's Republic of Korea
- ☒ KR Republic of Korea
- ☒ KZ Kazakhstan
- ☒ LC Saint Lucia
- ☒ LK Sri Lanka
- ☒ LR Liberia
- ☒ LS Lesotho
- ☒ LT Lithuania
- ☒ LU Luxembourg
- ☒ LV Latvia
- ☒ MD Republic of Moldova
- ☒ MG Madagascar
- ☒ MK The former Yugoslav Republic of Macedonia
- ☒ MN Mongolia
- ☒ MW Malawi
- ☒ MX Mexico
- ☒ NO Norway
- ☒ NZ New Zealand
- ☒ PL Poland
- ☒ PT Portugal
- ☒ RO Romania
- ☒ RU Russian Federation
- ☒ SD Sudan
- ☒ SE Sweden
- ☒ SG Singapore
- ☒ SI Slovenia
- ☒ SK Slovakia
- ☒ SL Sierra Leone
- ☒ TJ Tajikistan
- ☒ TM Turkmenistan
- ☒ TR Turkey
- ☒ TT Trinidad and Tobago
- ☒ UA Ukraine
- ☒ UG Uganda
- ☒ US United States of America
- ☒ UZ Uzbekistan
- ☒ VN Viet Nam
- ☒ YU Yugoslavia
- ☒ ZA South Africa
- ☒ ZW Zimbabwe

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

- ☒ CR Costa Rica
- ☒ DM Dominica
- ☒ TZ U.R. of Tanzania

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) –	–	–		
item (2)				
item (3)				

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): _____

** Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*
ISA/ EP

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*
Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets:**

request	:	4
description (excluding sequence listing part)	:	10
claims	:	3
abstract	:	1
drawings	:	6
sequence listing part of description	:	
Total number of sheets	:	24

This international application is **accompanied** by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

Figure of the drawings which should accompany the abstract: Fig. 1

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

BUDDE SCHOU & OSTENFELD A/S
by Leif Rørbøl

For receiving Office use only

1. Date of actual receipt of the purported international application:
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA/
6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
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United States Patent and Trademark
Office, PCT
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Arlington, VA 22202
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in its capacity as elected Office

Date of mailing (day/month/year) 13 June 2001 (13.06.01)	
International application No. PCT/DK99/00522	**Applicant's or agent's file reference** 60161/SGW/AW
International filing date (day/month/year) 04 October 1999 (04.10.99)	**Priority date** (day/month/year)
Applicant DAMGAARD, Lars, Riis et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

12 April 2001 (12.04.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Odile ALIU
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38